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The Co-occurrence of Cigarette Smoking and Bipolar Disorder: Phenomenology and Treatment Considerations

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Abstract

Objectives—Despite recent advances in understanding the causes and treatment of nicotine dependence among individuals with psychiatric disorders, smoking among individuals with bipolar disorder (BD) has received little attention. The goal of this review is to synthesize the literature on the epidemiology, consequences, and treatment of smoking and nicotine dependence among individuals with BD and to delineate a future research agenda.

Methods—We conducted a PubMed search of English-language articles using the search terms “bipolar disorder,” “mania,” “tobacco,” “nicotine,” “and “smoking,” followed by a manual search of the literature cited in the identified articles. Articles were chosen by the authors on the basis of their relevance to the topic areas covered in this selective review.

Results—Adults with BD are 2 to 3 times more likely to have started smoking and, on the basis of epidemiological data, may be less likely to initiate and/or maintain smoking abstinence than individuals without psychiatric disorders. Smoking cessation is achievable for individuals with BD, but challenges such as chronic mood dysregulation, high prevalence of alcohol and drug use, more severe nicotine dependence, and limited social support can make quitting more difficult. Effective treatments for tobacco cessation are available, but no controlled trials in smokers with BD have been conducted.

Conclusions—Cigarette smoking is a prevalent and devastating addiction among individuals with BD and should be addressed by mental health providers. Additional research on the mechanisms of, and optimal treatment for, smoking and nicotine dependence in this population is desperately needed.

Keywords

tobacco; nicotine; bipolar disorder; depression; mania

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Introduction

Cigarette smoking is significantly more prevalent among individuals with bipolar disorder (BD) than among individuals without the disorder (1,2) and has dire consequences. For example, a recent study examining mortality rates among consumers of public mental health services estimated that, on average, individuals with BD and other major mental illnesses die up to three decades earlier than their general population counterparts (3). Although some of these untimely deaths resulted from suicides or accidents, the most frequent causes of death were cancer, cardiovascular, cerebrovascular, and respiratory diseases—conditions for which tobacco use is a known cause of early mortality (4).

Despite the scope of the problem and the implications of tobacco use in BD, limited systematic research is available on this topic. Consequently, the purpose of this review is to synthesize the existing literature and delineate a research agenda, toward a goal of improving knowledge of the underlying mechanisms of, and treatment for, nicotine dependence in individuals with BD. Because smoking is the primary means by which tobacco is consumed and previous research on tobacco use among individuals with BD has focused almost exclusively on smoking, we restricted our review to cigarette smoking. In the sections that follow, we: 1) summarize the literature on prevalence and consequences of cigarette smoking among individuals with BD; 2) examine possible genetic, biological, and psychosocial risk factors that may explain the high prevalence of smoking in this population; 3) enumerate the challenges of smoking cessation and discuss implications for treatment; and 4) identify gaps in the literature as a means of guiding future research.

Methodology of the Literature Search

For this selective review, we conducted a PubMed search of English-language articles using the following search strategy: (bipolar disorder OR mania) AND (tobacco OR nicotine OR smoking). This search yielded 262 hits, the majority of which were not relevant to this review. Of the identified articles that were relevant and that we selected for inclusion, only 13 were empirical studies in which cigarette smoking among individuals with BD was the primary focus (1,2,5–15). Of note, 12 of these 13 studies were published after 2004, suggesting that attention to the relationship between smoking and BD may be increasing.

Epidemiology of Smoking and Nicotine Dependence in Individuals with Bipolar Disorder

Estimates of the prevalence rate of current smoking among individuals with BD range from 30% to 70% (1,6,16–19). Although some of this variability can be attributed to small sample sizes and non-representative clinical samples, even population-based prevalence studies have produced disparate findings. For example, data from the 1992–1993 National Comorbidity Survey (NCS) suggested that the prevalence of smoking in BD was 69% (16), whereas the more recent 2007 National Health Interview Survey (NHIS) showed a prevalence rate of 46% (19). Despite this variability in prevalence estimates, controlled population-based (16,19,20) and clinical studies (7–9,21) conducted in the U.S. and Europe have consistently demonstrated that the prevalence of smoking is approximately 2 to 3 times higher among individuals with BD than in the general population.

Epidemiologic data also suggest that the prevalence of smoking in BD is high relative to other Axis I psychiatric disorders. In the NCS study, the prevalence of current smoking in BD (69%) exceeded that of individuals with lifetime nonaffective psychosis (49%), drug abuse or dependence (49%), generalized anxiety disorder (46%), posttruamatic stress

disorder (45%), alcohol abuse or dependence (44%), panic attacks and phobias (36–40%), and major depression (37%) (16). However, the reliability of comparisons among the diagnostic groups in the NCS study are questionable due to the relatively small sample size within groups. In the more recent and larger NHIS study, individuals with BD were found to have a significantly lower smoking prevalence rate than individuals with schizophrenia (46% vs. 59%) (19). Although the NHIS data set is not without limitations (i.e., limited number of Axis I disorders assessed, use of self-reported diagnoses), the finding that there is a higher prevalence of smoking among individuals with schizophrenia than among those with BD has also been demonstrated in large clinical samples (17). Nonetheless, it appears that BD is among the Axis I psychiatric disorders with the highest prevalence of cigarette smoking and nicotine dependence.

The high prevalence rates of smoking among individuals with BD appear to be attributable to both increased likelihood of initiating smoking and decreased likelihood of successfully quitting. In terms of initiation, in the only controlled study of tobacco use in adolescents with BD, Wilens and colleagues (10) reported that adolescents with BD are more likely to initiate smoking than age-matched peers without psychiatric disorders (i.e., 22% vs. 4%). Additionally, the *lifetime* prevalence of smoking among individuals with BD is approximately 80%, which is roughly double that of the general population (16). Cross-sectional and retrospective data from several studies also indicate that individuals with BD are more likely than individuals in the general population to be heavy smokers (7,8) and to be nicotine dependent (20), which can make cessation more challenging. Indeed, although prospective data on smoking cessation are lacking, estimates of the proportion of ever-smoking individuals with BD who successfully quit is lower than the proportion of the general population who quit smoking (with estimates of 8–16% for individuals with BD vs. 33–43% for the general population) (7,16). Of course, these are differences in lifetime quit rates, which are not the same as differences in the likelihood of successful quitting on any given attempt.

Potential Mechanisms Underlying the Relationship between Smoking and Bipolar Disorder

Mechanisms underlying the relationship between smoking and BD are likely complex and multifactorial, including genetic and environmental factors as well as their interactions. Research on these mechanisms is sparse in BD, but several decades of research on the relationship between depression and smoking suggest causal pathways in both directions (22,23), and that these relationships may also be explained by common or correlated risk factors (24). In the sections that follow, we outline evidence suggesting that the co-occurrence of smoking and BD may also be attributable to bidirectional influences as well as common risk factors. In doing so, we draw upon the more developed literature on mechanisms underlying the relationship between depression and smoking to supplement the available literature on BD and smoking and to highlight potential avenues for further research.

BD increases risk of smoking/nicotine dependence

One potential explanation for the high rate of smoking among individuals with BD is that bipolar symptoms may increase the risk of initiating or maintaining regular smoking. Because of tobacco smoke's monoamine oxidase (MAO)-inhibiting effects (25) and nicotine's capacity to stimulate the release of neurotransmitters that improve mood and induce feelings of pleasure (e.g., serotonin and dopamine), the "self-medication hypothesis" has been invoked to explain the greater risk of smoking among individuals with depression. As described by Khantzian (26), this hypothesis suggests that an individual's preference for,

or use of, a specific substance of abuse is motivated by the propensity of that substance to pharmacologically alter an undesired emotional state.

In support of the self-medication hypothesis, depressed smokers are more likely than non-depressed smokers to report smoking as a means of reducing negative affect and increasing positive affect (27). Additionally, nicotine replacement reduces post-cessation negative affect in depressed smokers (28), and experimental evidence indicates that the mood-enhancing effects of nicotine are heightened in depressed smokers as compared to their non-depressed counterparts (29). It is not clear, however, whether these findings generalize to smokers with BD.

In addition to its effects on mood, nicotine also has a modest capacity to enhance cognitive functioning, including attention. In fact, self-medication of attentional deficits has been posited as one of the mechanisms underlying the high rate of smoking among individuals with attention-deficit/hyperactivity disorder (ADHD) (30,31). Given the high rate of co-occurring ADHD among individuals with BD (32) as well as the cognitive deficits that are evident both during and between affective episodes in BD (33), the cognitive enhancement associated with nicotine use may represent another form of self-medication underlying the relationship between smoking and BD. However, in the only study to date that has evaluated the relationship between smoking and cognitive performance in adults with BD (all of whom were euthymic at the time of testing), smokers scored higher on the subjective, but not the objective, assessments of cognitive functioning (11). Thus, although this was a small pilot study, these results suggest that the expectancies regarding cognitive benefits may be more influential in motivating individuals with BD to smoke than the actual effects of tobacco use on cognitive performance.

In addition to BD symptoms, medications used in the treatment of BD, such as certain antipsychotics and antiepileptics, may also enhance the risk of developing regular or dependent smoking. For example, among smokers with schizophrenia, nicotine has been demonstrated to offset some of the side effects associated with antipsychotic medications by improving performance on objective indicators of attention and memory (34). Additionally, treatment with higher dosages of antipsychotics has been linked to greater motivation to smoke for stimulatory effects in smokers with schizophrenia (35). Some medications may also impact smoking by altering the metabolism of nicotine, as suggested in a recent preliminary report indicating that carbamazepine may induce nicotine metabolism through its actions on CYP2A6 (36). Although it has not been conclusively demonstrated that medication-induced changes in nicotine metabolism alter smoking behavior, there is evidence that individuals who are faster metabolizers of nicotine tend to be heavier smokers (37), supporting the potential clinical significance of these findings.

A final consideration regarding the hypothesis that BD increases the risk of smoking is that, by virtue of having BD, individuals may be exposed to environments that are more conducive to smoking. For example, being in treatment settings where mental health professionals either implicitly or explicitly condone smoking and where a high proportion of patients and/or staff smoke are environmental influences that support initiation or continuation of smoking.

Smoking/nicotine dependence increases risk of BD

Another possible explanation for the high rates of smoking in BD is that smoking may increase the risk of developing BD. For example, smoking may lead to alterations in neurophysiology that unmask an underlying vulnerability to affective episodes. Consistent with this hypothesis, there is evidence from both preclinical and clinical studies to suggest that chronic exposure to nicotine may increase risk of developing depression by

desensitizing nicotinic acetylcholine receptors in the brain's limbic system (38). It has also been proposed that longer-term exposure to nicotine can induce depression through actions on serotonin pathways in the hippocampus, but smokers are protected from these effects as long as they continue to smoke (39).

Although there has been no systematic study of this phenomenon as it relates to onset of BD, it has been suggested that smoking cessation may precipitate an affective episode in some smokers who have already been diagnosed with BD. For example, one study that included a very small subsample (n=8) of smokers with BD demonstrated onset of depression following smoking cessation in 38% (n=3) of those individuals, which exceeded the incidence of emergent depression in smokers without depression histories (40). There are also rare case reports of episodes of mania coinciding with smoking cessation (41,42), and in one small (n=5), placebo-controlled trial of bupropion (Zyban®) for smoking cessation in BD, 40% (n=2, both of whom were taking placebo) of the participants developed hypomania during the treatment period (12). However, the quality of evidence from case reports and small-sample studies such as this one is low, and it would be premature to conclude from these reports that smoking cessation is a precipitant of affective episodes in smokers with BD. Rather, these results suggest that this area warrants further study.

BD and smoking share common risk factors

BD and smoking may also be linked through common risk factors, including both genetic and environmental influences. Regarding shared genetic risks, several overlapping candidate genes for BD and smoking have been identified, including genes that encode: 1) catechol-O-methyltransferase (COMT); 2) the dopamine transporter; and 3) the serotonin transporter (13). Moreover, a number of neurochemical systems have been implicated in both BD and nicotine dependence, with most attention focused on dopamine, serotonin and norepinephrine (43–48).

Recent studies in both patients with BD and tobacco smokers have demonstrated structural and functional differences in overlapping brain regions across the two groups. Specifically, the anterior limbic network—a system which is intimately related to functions and traits which are central to BD (e.g. impulsivity and affective regulation in the context of a manic episode) (49) and which are hypothesized to relate to the pathophysiology of nicotine dependence (e.g. dysfunctional reward processing) (50)—has received significant attention. Several prefrontal subregions, including the dorsolateral prefrontal cortex, ventral prefrontal cortex, and anterior cingulate cortex exhibit volumetric differences among adults with BD and among smokers relative to comparison subjects (51–55). In terms of functional differences, functional magnetic resonance imaging (fMRI) studies of patients with BD have demonstrated increased brain activation in important regions of the cortico-limbic pathways responsible for emotional regulation (i.e. prefrontal cortex, anterior cingulate cortex, amygdala, thalamus and striatum) (see reference 49 for recent review). Similarly, fMRI studies of nicotine dependent individuals without BD have observed differences in the functional activation of many of these mesocorticolimbic structures, often in response to fMRI tasks involving smoking cues (56,57).

In addition to these biological explanations for the high rates of smoking among individuals with BD, potential shared environmental risk factors for BD and smoking likely contribute to their co-occurrence. For example, abuse and other forms of childhood adversity have been linked to a greater risk of developing psychiatric disorders as well as daily smoking (58). Additionally, alcohol and illicit drug use have been implicated in both the development of regular smoking and nicotine dependence (59,60) and in the onset of BD (61,62).

In summary, although the evidence in individuals with BD is sparse, there are some indications that BD may be similar to depression in the mechanisms underlying its relationship with smoking. That is, the relationship is likely bidirectional, at least partly attributable to shared risk factors, and includes genetic/biological and environmental risks. Given the substantial gaps in the literature, however, many questions remain. For example, the extent to which individuals with BD might smoke as a means of self-medication and the extent to which tobacco use might influence the development of BD symptoms have yet to be evaluated. Prospective and longitudinal studies are needed to: 1) evaluate the temporal ordering of smoking and BD onset in order to establish directionality of the relationship; 2) determine the extent to which smoking frequency and intensity are affected by mood state and mood state is affected by smoking; and 3) identify biological risk factors for tobacco smoking in patients with BD as well as neural correlates of smoking cessation treatment response. The addition of more detailed assessments of smoking and nicotine dependence to ongoing and new longitudinal studies of adolescents and adults with BD would help to begin answering some of these questions, as would an increased focus on the process of quitting among smokers with BD who attempt cessation.

Consequences of Smoking

Morbidity and mortality

Cigarette smoking is a leading cause of mortality in the United States and worldwide, and, as noted previously, it contributes to the significant discrepancies in life expectancy between individuals with major mental illnesses such as BD and the general population (3,17). In addition to dying decades earlier, individuals with BD are also more likely to be living with chronic medical illnesses than individuals without the disorder (63). These illnesses are often known to be caused or exacerbated by cigarette smoking and include conditions such as chronic obstructive pulmonary disease, asthma, hypertension, and cardiovascular disease (64,65). In addition to their greater likelihood of having these diseases, individuals with BD also appear to be developing them at substantially younger ages (63). Moreover, high rates of obesity and the metabolic syndrome are also associated with BD (66–68), and the addition of cigarette smoking to these conditions creates a dangerous combination of risk factors for premature death (69).

Effects of tobacco smoke on the metabolism of psychotropic medications

Polycyclic aromatic hydrocarbons in tobacco smoke increase the metabolism of some psychotropic medications through actions on the cytochrome P450 system, specifically through induction of the CYP1A2 enzyme (70). This enzyme metabolizes several antipsychotic and antidepressant drugs frequently used in BD patients, including olanzapine (71), clozapine (72), haloperidol (70), and fluvoxamine (73). Cigarette smokers may require as much as a 50% increase in dose of these medications in order to gain symptom relief (74). Notably, heavy smoking is not a prerequisite for such dose adjustments, as the pharmacokinetics of clozapine and olanzapine in smokers who consume 7–12 cigarettes per day are statistically indistinguishable from that of smokers who consume over one pack per day (74).

If tobacco use is not considered when establishing a dosing regimen for medications that interact with tobacco smoke, treatment outcomes may be worsened. For example, one recent study found that smokers had worse treatment outcomes than nonsmokers when taking olanzapine or haloperidol, but not when taking divalproex (which is not metabolized by CYP1A2) or placebo (6). Additionally, case report level evidence suggests that a substantive increase in smoking can lead to an increase in psychiatric symptoms among individuals with

BD who are taking olanzapine, ostensibly due to the resultant reduction in medication levels (75).

The impact of smoking cessation on individuals taking these medications is also important to consider, as a reduction or discontinuation of smoking may result in substantial increases in plasma levels and an increased likelihood of adverse reactions or toxicity. Several published case reports in this area have included accounts of increased extrapyramidal side effects, seizures, sedation, and worsening of psychiatric symptoms that commenced with smoking cessation and remitted with a reduction in clozapine or olanzapine dosage (75,76). Therefore, clinicians must be vigilant in monitoring adverse effects and adjusting medication levels as needed when patients are trying to quit smoking.

Effects of nicotine on the pharmacodynamics of other medications

In addition to the pharmacokinetic effects of tobacco smoke on the metabolism of certain psychotropic medications, nicotine can pharmacodynamically impact the efficacy of some medications used in the treatment of psychiatric or physical conditions. For example, nicotine's activation of the sympathetic nervous system may reduce the sedating effects of benzodiazepines and the capacity of β-blockers to lower heart rate and blood pressure (70). Individuals who use tobacco or nicotine replacement therapies may require higher dosages of these medications, and conversely, individuals who discontinue use of nicotine-containing products may require a dosage reduction.

In summary, the negative impact of tobacco use on the lives of people with BD is far-reaching, yet tobacco's detrimental effects on both the quantity and the quality of life among individuals with BD are entirely preventable. Nonetheless, there could be several impediments to successful tobacco cessation in this group of smokers. In the sections that follow, we review some of the likely challenges and outline the principles of evidence-based tobacco treatment for tobacco cessation. We also discuss some unique treatment considerations for this special population of smokers, highlighting areas where additional research is needed to guide clinical practice.

Treatment Challenges

Although there are no adequately-sized, prospective tobacco cessation studies in smokers with BD, evidence from epidemiologic studies suggests that quit rates for smokers with BD may be worse than for smokers without the disorder (7,16). These low quit rates could reflect the unique challenges that smokers with BD face when they attempt to quit, which we review in this section (see Table 1 for a summary). The current dearth of research focusing specifically on smokers with BD requires some selective extrapolation from the literature on smoking cessation among individuals with depression and schizophrenia. Because of the uncertain generalizability of these findings to smokers with BD, conclusions derived from them should be considered tentative.

Symptoms of BD

Although the evidence is not unanimous, prior research has demonstrated that smoking is correlated with more severe mood symptoms in BD, including more severe symptoms of depression, rapid cycling, greater overall illness severity, and increased likelihood of suicidal ideation and behavior (1,14,15). The influence of mood state on the success of a smoking cessation attempt among individuals with BD has not been investigated, but previous research suggests that depression is a risk factor for smoking cessation treatment failure (28,77). Although this finding has been disputed (78), it may be specific to multiple major depressive episodes (40) that typify recurrent major depressive disorder or bipolar disorder (1) rather than single-episode major depressive disorder. The link between recurrent

depressive episodes and reduced smoking cessation success may be attributable to the increased likelihood of depressive symptoms either preceding or following attempts to quit smoking (77, 79) and the use of smoking as a form of coping with negative affect or mood (27,28,80). In fact, there is strong evidence linking smoking relapse to post-quit negative affect (81), and smokers with a history of depression may be particularly vulnerable to affect-related relapse.

The effects of mania or hypomania on a smoking cessation attempt have not been as systematically evaluated as depression has been, but there is reason to believe that these mood states may also represent a threat to smoking abstinence. For example, the impulsivity that is characteristic of mania and hypomania is a likely barrier to cessation. Indeed, prior research with non-psychiatric smokers has demonstrated a relationship between impulsivity and smoking relapse (82).

Alcohol and drug use

Numerous studies have documented strong relationships among cigarette smoking, alcohol and marijuana use, and BD. We previously suggested that recent use of marijuana and alcohol was two to three times more prevalent among bipolar smokers as compared to nonsmokers (2). Additionally, over half (53%) of participants who currently smoked cigarettes met lifetime criteria for a cannabis use disorder (vs. 12% of the nonsmokers), and over one-third (34%) met criteria for an alcohol use disorder (vs. 15% of the nonsmokers) (2). Ostacher and colleagues (15) also found that individuals with BD who had lifetime alcohol and other substance use disorders had 2 to 3 times the odds of being an ever-smoker as compared to those without a substance use disorder history.

Although there have been no prospective studies of the effects of alcohol and drug use on smoking cessation in individuals with BD, studies involving smokers without psychiatric disorders have demonstrated that both alcohol and cannabis use interfere with smoking cessation. Laboratory evidence suggests that alcohol use triggers craving to smoke cigarettes (83), and alcohol consumption has been linked to smoking relapse in a number of smoking cessation studies (84–86). Likewise, cannabis use has been linked to a decreased likelihood of quitting smoking in both epidemiologic (87) and treatment (88) studies. Finally, alcohol and drug use may indirectly threaten the success of smoking cessation efforts by exacerbating psychiatric symptoms (89).

Nicotine dependence and nicotine withdrawal

Use of nicotine, the primary addictive substance in tobacco, can lead to a state of dependence similar to other substances of abuse. This includes a withdrawal syndrome marked by symptoms such as irritability, anxiety, dysphoria, impaired concentration, and increased appetite or weight gain. Nicotine dependence and withdrawal are critical factors in the maintenance of smoking, and more severe dependence or withdrawal are associated with more difficulty in quitting smoking (90). Smokers with psychiatric disorders—most notably those with serious mental illness and/or substance use disorders-- tend to present with more severe nicotine dependence and nicotine withdrawal than smokers without these illnesses (91–93). Given that some studies have found that ability to quit smoking is inversely associated with the amount of cigarettes smoked (94), the higher prevalence of heavy, daily smoking among individuals with BD (7) represents an additional challenge to cessation. In a related fashion, one aspect of nicotine withdrawal—the increased appetite and weight gain experienced by the majority of people who quit (95)—may be especially problematic for smokers with BD. Weight concerns are common among smokers who are preparing to quit, especially among women, and these concerns can translate into failure to initiate or sustain a quit attempt (96–98). Because weight gain is also a side effect of several of the medications

used to treat BD, additional weight gain subsequent to smoking cessation may not be well-tolerated.

Social support for quitting

Lack of support for quitting and a high density of smokers in one's social environment are two common socioenvironmental barriers to successful smoking cessation, and both of these factors are likely to plague smokers with BD. In a preliminary study of a smoking cessation intervention for mental health outpatients, participants reported a perceived lack of support from partners for any behavioral change, including smoking cessation (99). It is likely that a portion of the partners in this study who were perceived as unsupportive were smokers themselves, and the presence of smokers in the household is a relatively robust predictor of a poor smoking cessation outcome (99–103).

Beliefs and practices of mental health treatment providers

Mental health professionals who treat patients with BD are uniquely positioned to offer support and treatment for smoking cessation, yet research indicates that they seldom do so. For example, a study of psychiatrists' practices with respect to tobacco cessation interventions suggested that providers were fairly conscientious in assessing patients' smoking status (status identified in 76% of visits), but not in providing cessation counseling (12% of visits) or pharmacotherapy (0% of visits) (104). Similarly, a survey of psychologists indicated that only 29% of respondents asked all patients if they smoke, and only 31% advised all of their patients to quit if they were aware that the patient smoked (105).

Many clinicians report concerns that cessation of smoking will lead to worsening of psychiatric symptoms; however, there is little empirical evidence to support this contention. For example, several studies found that smoking cessation did not lead to a clinically significant deterioration in psychiatric status among individuals with schizophrenia (106,107). With regard to depression, although it is common for recent quitters to experience short-lived dysphoria as part of nicotine withdrawal, onset of a major depressive episode is considerably less common, with estimates of the incidence generally ranging from less than 1% to 7% (77,108,109). Onset of a major depressive episode may occur more frequently in smokers with a history of major depressive disorder (MDD) (108), but not all studies agree on this point (110). As noted previously, although there have been a few published case reports (41,42) and treatment studies involving only a handful of smokers with BD (12,40), the hypothesis that smoking cessation worsens BD symptoms has not been tested and seems unlikely.

At the organizational level, despite the potential of mental health treatment programs to facilitate change in health behaviors, cigarette smoking has historically been ignored or, in some cases, even encouraged in treatment settings. However, these historical trends are changing, and many treatment programs have become tobacco-free and are providing tobacco cessation treatment as part of the clinical programming. Reports of successful transitions to tobacco-free facilities have been accumulating in the literature, and there is evidence that, when planned and implemented thoughtfully, this transition does not adversely affect patients or staff. In fact, some studies have documented improvements in patient behavior and patient-staff interactions as a result of smoke-free policies (111), and a tobacco-free environment may increase patients' self-efficacy and intention to quit (112). At the same time, a high prevalence of patients who smoke; treatment providers who are reluctant to address smoking, particularly if they are smokers themselves; and the lack of staff training in tobacco treatment remain critical barriers to promoting smoking cessation in some mental health treatment settings (113).

In summary, smokers with BD are likely to experience greater challenges to tobacco cessation than the average smoker, including chronic mood dysregulation, more severe nicotine dependence, and limited support for quitting. However, these challenges can be overcome, and the extent of their impact on the outcome of a cessation attempt in smokers with BD has not yet been examined. Regardless, mental health and/or addictions treatment providers have the expertise to assist smokers with BD in overcoming these challenges, yet research suggests that these individuals may not be consistently addressing clients' tobacco use. Integration of tobacco treatment into mental health and addictions treatment would therefore expand the current reach of efforts to reduce the prevalence of smoking among people with BD and other psychiatric disorders, and reduce the disproportionate burden of tobacco-related disease borne by these individuals.

Smoking Cessation Interventions for Individuals with BD

Effective interventions for smoking cessation range from brief advice to quit up to combined behavioral and pharmacological treatments. The latter is designed to target both the psychosocial and biological factors that are involved in tobacco addiction and is currently considered to be the gold standard of smoking cessation treatment (90). A range of behavioral therapy and pharmacotherapy approaches are currently available to assist smokers in quitting (see the recently-updated clinical practice guidelines [90] for a comprehensive summary of these interventions and the evidence that supports their use). Importantly, studies examining the efficacy of these interventions for smokers with psychiatric and substance use disorders demonstrate that these treatments are effective in this special population of smokers (114,115). In this section, we sketch the major principles of pharmacotherapy and behavioral therapy for smoking cessation and discuss treatment considerations for smokers with BD.

Pharmacotherapy

Current treatment guidelines (90) suggest that all smokers wishing to quit should be offered pharmacotherapy. There are several pharmacotherapies approved by the FDA as first-line treatments for smoking cessation: nicotine replacement therapy (NRT), bupropion sustained-release, and varenicline (Chantix/Champix®) (see Table 2 for an overview of these agents, their efficacy in smokers without mental illness, and considerations for use in smokers with BD). At present, the safety and efficacy profiles of these smoking cessation aids for individuals with BD are unclear due to the lack of controlled trials that include this group of smokers. Consequently, those who prescribe these agents should keep in mind that there may be unknown risks and/or benefits associated with these medications in populations of smokers who are typically excluded from clinical trials, including smokers with BD.

NRT is available in a variety of formulations (i.e., as over-the-counter lozenge, gum, or patch; and prescription-only inhaler and nasal spray), all of which are of similar efficacy (90). Combination NRT, in which a shorter-acting formulation such as nicotine gum or nasal spray is added onto longer-acting nicotine patch, has demonstrated some improved efficacy beyond single-formulation NRT in controlled clinical trials among smokers without psychiatric disorders (90) and may be beneficial to heavier smokers by providing a greater percentage of nicotine replacement. Similarly, anecdotal clinical reports suggest that extended treatment with NRT (e.g., up to 6 months) may confer some additional benefits for smokers with psychiatric disorders (94), although extended treatment has not been shown to improve long-term smoking cessation outcomes in the general population (90), and this hypothesis has yet to be tested in smokers with BD. Additionally, prior studies have demonstrated that adequate treatment with nicotine gum can delay, but not entirely prevent, postcessation weight gain (69), one of the likely challenges to smoking cessation in this population.

Bupropion, an antidepressant and nicotinic acetylcholine receptor antagonist, can be used either alone or off-label in combination with NRT as a smoking cessation aid. By itself, bupropion is of similar efficacy to single-formulation NRT, with the combination of bupropion and NRT appearing to be more efficacious than bupropion alone (116). Like nicotine gum, bupropion has also been found to delay postcessation weight gain, thereby reducing one of the potential barriers to smoking cessation (69). One complicating factor related to the use of bupropion for smokers with BD include its potential interaction with other psychotropic medications (e.g., carbamazepine, which induces metabolism of bupropion and decreases plasma levels substantially). (117) There is also the possibility of inducing mood destabilization, although this has been observed only in a small proportion of individuals with BD who were taking the medication as an antidepressant (118,119), and there is no strong evidence to suggest that bupropion induces mania when used as a smoking cessation agent in stably treated BD. Additionally, bupropion currently carries an FDA-mandated boxed warning due, in part, to postmarketing reports of increased risk of neuropsychiatric side effects such as agitation, depressed mood, and suicidality. Thus, individuals with BD who are taking bupropion as a smoking cessation aid should be closely monitored for signs of accelerated mood cycling, and this medication should only be used in conjunction with a mood stabilizing agent. Also, because of the increased seizure risk associated with this medication, it should be used cautiously in combination with other psychotropic medications that increase seizure risk, including some antipsychotics (46).

Varenicline, an $\alpha_4\beta_2$ nicotinic receptor partial agonist, is the most recent addition to the arsenal of smoking cessation pharmacotherapies. Evidence to date suggests that varenicline is among the most efficacious of the available smoking cessation medications (90,120,121). However, there have been reports of exacerbation of psychiatric symptoms associated with varenicline use that prompted a recent warning to this effect by the FDA, and several anecdotal reports of worsening of symptoms of BD have appeared in the literature (122–124). Thus, as with bupropion, smokers with BD who are using varenicline should be monitored carefully for worsening of psychiatric symptoms.

Behavioral interventions

In addition to pharmacotherapy, behavioral interventions also improve the probability of quitting smoking, particularly when used in combination with pharmacotherapy (90). Targeted behavioral interventions that are designed to enhance the efficacy of treatment in psychiatric populations have been developed and tested (125–127), but current evidence is insufficient to recommend these approaches as alternatives to standard counseling. Despite the current unavailability of widespread evidence to support their use, pilot work investigating targeted interventions with specialized content have shown some promise for smokers with psychiatric disorders including depression (125,126,128) and substance use disorders (129). For example, cognitive-behavioral therapy (CBT)-based mood management interventions for smoking cessation have been tested in smokers with a history of depression (125,126,128,130) and, although they were not effective in smokers with a history of single-episode depression, they were effective for smokers who had experienced recurrent depressive episodes in the past (125,131). Given that the majority of individuals with bipolar disorder experience recurrent episodes of depression (1), such an intervention may hold promise in this group as well, but this proposition has yet to be tested.

Behavioral intervention intensity

In general, increasing amounts of treatment contact time are associated with increased rates of smoking cessation success (90). Psychosocial interventions of greater intensity may be particularly important as an adjunct to pharmacotherapy for smokers with a history of depression (126,128). Although some individuals with BD may benefit from brief advice

and support alone, they should also be encouraged to consider options for more intensive behavioral interventions, particularly if initial attempts at quitting without intensive support are unsuccessful.

Timing of Treatment

The optimal timing of smoking cessation treatment for individuals with substance-related and other psychiatric disorders has been discussed extensively, but there have been few systematic investigations to date that were designed to answer this important question (113,132). Thus, there is little empirical guidance to determine the optimal timing of a smoking cessation attempt for individuals with BD, and clinical judgment is needed to guide decisions about the best time to intervene regarding tobacco cessation. It is our position that periods of relative stability or euthymia are the ideal points at which to encourage tobacco cessation (133). At the same time, it is ill-advised to discourage a smoker who expresses interest quitting from doing so unless there is clear reason to believe that such an action carries a strong risk of untoward effects and should consequently be delayed. Examples of such times might include points at which medication dosages are being titrated or when there has been a recent increase in psychiatric symptoms.

In summary, a number of effective treatments for tobacco cessation are available to aid smokers who want to quit, and there is solid evidence that these treatments can and do help individuals with psychiatric disorders quit smoking. At the same time, additional research examining their safety and efficacy in smokers with BD would provide better guidance on treatment decisions for this group. Because of the current boxed warnings for bupropion and varenicline, smokers with BD who are using these as cessation agents should be monitored for signs of worsening psychiatric status. Pharmacotherapy provides the best outcomes when used in combination with counseling, and, in general, greater amounts of counseling are associated with increasing odds of successful quitting. However, brief advice to quit is effective and should be provided to all smokers, consistent with Clinical Practice Guideline recommendations (90). More research is needed to determine the optimal timing of treatment, intensity of counseling, and efficacy of targeted treatment approaches for smokers with BD.

Conclusions

Much like alcohol and illicit drug use disorders, cigarette smoking is a prevalent and devastating co-occurring condition in individuals with BD. In addition to the challenges faced by all smokers when they try to quit, smokers with BD face additional hurdles related to the core features of the disorder (i.e., dysregulation of mood) as well as its correlates (e.g., co-occurring alcohol and drug use, heavy smoking/nicotine dependence) during a cessation attempt. However, the benefits of tobacco cessation are innumerable, and prior demonstrations that smokers with other mental illnesses such as depression and schizophrenia can quit smoking successfully with the assistance of evidence-based treatments are encouraging. Nonetheless, there is a significant need for research to identify the best approaches to facilitate long-term smoking abstinence for smokers with BD in order to reduce the prevalence and consequences of this dangerous addiction.

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References

1. Waxmonsky JA, Thomas MR, Miklowitz DJ, Allen MH, Wisniewski SR, Zhang H, Ostacher MJ, Fossey MD. Prevalence and correlates of tobacco use in bipolar disorder: data from the first 2000 participants in the Systematic Treatment Enhancement Program. Gen Hosp Psychiatry. 2005; 27:321–328. [PubMed: 16168792]
2. Heffner JL, DelBello MP, Fleck DE, Anthenelli RM, Strakowski SM. Cigarette smoking among individuals with bipolar disorder: association with ages-at-onset of alcohol and marijuana use. Bipolar Disord. 2008; 10:838–845. [PubMed: 19032716]
3. Colton, CW.; Manderscheid, RW. Congruencies in increased mortality rates, years of potential life lost, and causes of death among public mental health clients in eight states. Prev Chronic Dis [serial online]. 2006 Apr. Available from: URL: http.//www.cdc.gov/pcd/issues/2006/apr/05_0180.htm
4. United States Department of Health and Human Services (USDHHS). The health consequences of smoking: a report of the surgeon general. US Department of Health and Human Services, Public Health Service, Office of the Surgeon General; 2004.
5. Baethge C, Tondo L, Lepri B, Baldessarinin RJ. Coffee and cigarette use: association with suicidal acts in 352 Sardinian bipolar disorder patients. Bipolar Disord. 2009; 11:494–503. [PubMed: 19624388]
6. Berk M, Ng F, Wang WV, Tohen M, Lubman DI, Vieta E, Dodd S. Going up in smoke: tobacco smoking is associated with worse treatment outcomes in mania. J Affect Disord. 2008; 110:126–134. [PubMed: 18280579]
7. Diaz FJ, James D, Botts S, Maw L, Susce MT, de Leon J. Tobacco smoking behaviors in bipolar disorder: a comparison of the general population, schizophrenia, and major depression. Bipolar Disord. 2009; 11:154–165. [PubMed: 19267698]
8. Gonzalez-Pinto A, Gutierrez M, Ezcurra J, Aizpuru F, Mosquera F, Lopez P, de Leon J. Tobacco smoking and bipolar disorder. J Clin Psychiatry. 1998; 59:225–228. [PubMed: 9632031]
9. Itkin O, Nemets B, Einat H. Smoking habits in bipolar and schizophrenic outpatients in southern Israel. J Clin Psychiatry. 2001; 62:269–272. [PubMed: 11379841]
10. Wilens TE, Biederman J, Adamson JJ, Henin A, Sgambati S, Gignac M, et al. Further evidence of an association between adolescent bipolar disorder with smoking and substance use disorders: a controlled study. Drug Alc Depend. 2008; 95:188–198.
11. Law CWY, Soczynska JK, Woldeyohannes HO, Miranda A, Brooks JO, McIntyre RS. Relation between cigarette smoking and cognitive function in euthymic individuals with bipolar disorder. Pharmacol Biochem Behav. 2009; 92:12–16. [PubMed: 18976682]
12. Weinberger AH, Vessicchio JC, Sacco KA, Creeden CL, Chengappa KNR, George TP. A preliminary study of sustained-release bupropion for smoking cessation in bipolar disorder. J Clin Psychopharmacol. 2008; 28:584–587. [PubMed: 18794666]
13. McEachin RC, Saccone NL, Saccone SF, Kleyman-Smith YD, Kar T, Kare RK, Ade AS, Sartor MA, Cavalcoli JD, McInnis MG. Modeling complex genetic and environmental influences on comorbid bipolar disorder with tobacco use disorder. BMC Med Genet. 2010; 11:14. [PubMed: 20102619]
14. Goldstein BI, Birmaher B, Axelson DA, Goldstein TR, Esposito-Smythers C, Strober MA, et al. Significance of cigarette smoking among youths with bipolar disorder. Am J Addictions. 2008; 17:364–371.
15. Ostacher MJ, Nierenberg AA, Perlis RH, Eidelman P, Borrelli DJ, Tran TB, et al. The relationship between smoking and suicidal behavior, comorbidity, and course of illness in bipolar disorder. J Clin Psychiatry. 2006; 67:1907–1911. [PubMed: 17194268]
16. Lasser K, Boyd JW, Woolhandler S, Himmelstein DU, McCormick D, Bor DH. Smoking and mental illness: a population-based prevalence study. JAMA. 2000; 284:2606–2610. [PubMed: 11086367]
17. Kilbourne AM, Morden NE, Austin K, Ilgen M, McCarthy JF, Dalack B, Blow FC. Excess heart-disease-related mortality in a national study of patients with mental disorders: identifying modifiable risk factors. Gen Hosp Psychiatry. 2009; 31:555–563. [PubMed: 19892214]

18. Vanable PA, Carey MP, Carey KB, Maisto SA. Smoking among psychiatric outpatients: relationship to substance use, diagnosis, and illness severity. Psychol Addictive Behav. 2003; 17:259–265.
19. McClave AK, McKnight-Eily LR, Davis SP, Dube SR. Smoking characteristics of adults with selected lifetime mental illnesses: results from the 2007 National Health Interview Survey. Am J Public Health. 2010; 100:2464–2472. [PubMed: 20966369]
20. Grant BF, Stinson FS, Hasin DS, Dawson DA, Chou SP, Ruan WJ, Huang B. Prevalence, correlates, and comorbidity of bipolar I disorder and axis I and II disorder: results from the National Epidemiologic Survey on Alcohol and Related Conditions. J Clin Psychiatry. 2005; 66:1205–1215. [PubMed: 16259532]
21. Döme P, Rihmer Z, Gonda X, Pestality P, Kovács G, Teleki Z, Mandl P. Cigarette smoking and psychiatric disorders in Hungary. Int J Psychiatry Clin Practice. 2005; 9:145–148.
22. Boden JM, Fergusson DM, Horwood LJ. Cigarette smoking and depression: tests of causal linkages using a longitudinal birth cohort. Br J Psychiatry. 2010; 196:440–446. [PubMed: 20513853]
23. McKenzie M, Olsson CA, Jorm AF, Romaniuk H, Patton GC. Association of adolescent symptoms of depression and anxiety with daily smoking and nicotine dependence in young adulthood: findings from a 10-year longitudinal study. Addiction. 2010; 105:1652–1659. [PubMed: 20707783]
24. Breslau N, Peterson EL, Schultz LR, Chilcoat HD, Andreski P. Major depression and stages of smoking: a longitudinal investigation. Arch Gen Psychiatry. 1998; 55:161–166. [PubMed: 9477930]
25. Berlin I, Anthenelli RM. Monoamine oxidases and tobacco smoking. Int J Neuropsychopharmacol. 2001; 4:33–42. [PubMed: 11343627]
26. Khantzian EJ. The self medication hypothesis of addictive disorders: focus on heroin and cocaine dependence. Am J Psychiatry. 1985; 142:1259–1264. [PubMed: 3904487]
27. Lerman C, Audrain J, Orleans CT, Boyd R, Gold K, Main D, Caporaso N. Investigation of mechanisms linking depressed mood to nicotine dependence. Addict Behav. 1996; 21:9–19. [PubMed: 8729703]
28. Kinnunen T, Doherty K, Militello FS, Garvey AJ. Depression and smoking cessation: Characteristics of depressed smokers and effects of nicotine replacement. J Consult Clin Psychol. 1996; 64:791–798. [PubMed: 8803370]
29. Spring B, Werth Cook J, Appelhans B, Maloney A, Richmond M, Vaughn J, Vanderveen J, Hedeker D. Nicotine effects on affective response in depression-prone smokers. Psychopharmacol. 2008; 196:461–471.
30. Gehricke J-G, Loughlin SE, Whalen CK, Potkin SG, Fallon JH, Jammer JH, Jamner LD, Belluzzi JD, Leslie FM. Smoking to self-medicate attentional and emotional dysfunctions. Nicotine Tob Res. 2007; 9:S523–S536. [PubMed: 18067030]
31. Lerman C, Audrain J, Tercyak K, Hawk LW, Bush A, Crystal-Mansour S, Rose C, Niaura R, Epstein LH. Attention-deficit hyperactivity disorder (ADHD) symptoms and smoking patterns among participants in a smoking cessation program. Nicotine Tob Res. 2001; 3:353–359. [PubMed: 11694203]
32. Singh MK, DelBello MP, Kowatch RA, Strakowski SM. Co-occurrence of bipolar and attention-deficit hyperactivity disorders in children. Bipolar Disord. 2006; 8:710–720. [PubMed: 17156157]
33. Kurtz MM, Gerraty RT. A meta-analytic investigation of neurocognitive deficits in bipolar illness: profile and effects of clinical state. Neuropsychology. 2009; 23:551–562. [PubMed: 19702409]
34. Levin ED, Wilson W, Rose JE, McEvoy J. Nicotine-haloperidol interactions and cognitive performance in schizophrenics. Neuropsychopharmacology. 1996; 15:429–436. [PubMed: 8914115]
35. Barr AM, Prochyshyn RM, Hui P, Johnson JL, Honer WG. Self-reported motivation to smoke in schizophrenia is related to antipsychotic drug treatment. Schizophr Res. 2008; 100:252–260. [PubMed: 18178062]

36. Williams JM, Gandhi KK, Benowitz NL. Carbamazepine but not valproate induces CYP2A6 activity in smokers with mental illness. Cancer Epidemiol Biomarkers Prev. 2010; 19:2582–2589. [PubMed: 20719908]
37. Falcone M, Jepson C, Benowitz N, Bergen AW, Pinto A, Wileyto EP, Baldwin D, Tyndale RF, Lerman C, Ray R. Association of the nicotine metabolite ratio and CHRNA5/CHRNA3 polymorphisms with smoking rate among treatment-seeking smokers. Nicotine Tob Res. 2011 (in press).
38. Mineur YS, Picciotto MR. Biological basis for the co-morbidity between smoking and mood disorders. J Dual Diagn. 2009; 5:122–130. [PubMed: 20046987]
39. Balfour DJK, Ridley DL. The effects of nicotine on neural pathways implicated in depression: a factor in nicotine addiction? Pharmacol Biochem Behav. 2000; 66:79–85. [PubMed: 10837846]
40. Glassman AH, Covey LS, Dalack GW, Stetner F, Rivelli SK, Fleiss J, Cooper TB. Smoking cessation, clonidine, and vulnerability to nicotine among dependent smokers. Clin Pharmacol Ther. 1993; 54:670–679. [PubMed: 8275622]
41. Labbate LA. Nicotine cessation, mania, and depression. Am J Psychiatry. 1992; 149:708. [PubMed: 1514953]
42. Benazzi F. Severe mania following abrupt nicotine withdrawal. Am J Psychiatry. 1989; 146:1641. [PubMed: 2486194]
43. Linnoila M, Karoum F, Potter WZ. Effects of antidepressant treatments on dopamine turnover in depressed patients. Arch Gen Psychiatry. 1983; 40:1015–7. [PubMed: 6225405]
44. Post RM, Rubinow DR, Uhde TW, Roy-Byrne PP, Linnoila M, Rosoff A, Cowdry R. Dysphoric mania. Clinical and biological correlates. Arch Gen Psychiatry. 1989; 46:353–8. [PubMed: 2930331]
45. Geracioti TD, West SA, Baker DG, Hill KK, Ekhator NN, Wortman MD, Keck PE, Norman AB. Low CSF Concentration of a Dopamine Metabolite in Tobacco Smokers. Am J Psychiatry. 156:130–132. [PubMed: 9892309]
46. Anthenelli, RM.; Hill, KK.; Ekhator, NN.; Baker, DG.; Maxwell, RA.; Geracioti, TD. A preliminary evaluation of cigarette smoking's effects on cerebrospinal fluid 5-hydroxyindolacetic acid concentrations. 7th Annual Meeting of the Society for Research on Nicotine and Tobacco; W.A. Seattle. 2001.
47. Sharma A, Brody AL. In vivo brain imaging of human exposure to nicotine and tobacco. Handb Exp Pharmacol. 2009; 192:145–71. [PubMed: 19184649]
48. Strawn JR, Ekhator NN, Anthenelli RM, Baker DG, Maxwell RA, Hill KK, Geracioti TD. Intra- and inter-individual relationships between central and peripheral serotonergic activity in humans: a serial cerebrospinal fluid sampling study. Life Sci. 2002; 71:1219–25. [PubMed: 12095542]
49. Cerullo MA, Adler CM, Delbello MP, Strakowski SM. The functional neuroanatomy of bipolar disorder. Int Rev Psychiatry. 2009; 21:314–22. [PubMed: 20374146]
50. Gamberino WC, Gold MS. Neurobiology of tobacco smoking and other addictive disorders. Psychiatr Clin North Am. 1999 Jun.22:301–12. [PubMed: 10385935]
51. Brody AL, Mandelkern MA, Jarvik ME, Lee GS, Smith EC, Huang JC, Bota RG, Bartzokis G, London ED. Differences between smokers and nonsmokers in regional gray matter volumes and densities. Biol Psychiatry. 2004; 55:77–84. [PubMed: 14706428]
52. Lopez-Larson MP, DelBello MP, Zimmerman ME, Schwiers ML, Strakowski SM. Regional prefrontal gray and white matter abnormalities in bipolar disorder. Biol Psychiatry. 2002; 52:93–100. [PubMed: 12114000]
53. Sax KW, Strakowski SM, Zimmerman ME, DelBello MP, Keck PE Jr, Hawkins JM. Frontosubcortical neuroanatomy and the continuous performance test in mania. Am J Psychiatry. 1999; 156:139–141. [PubMed: 9892312]
54. Frangou S. The Maudsley Bipolar Disorder Project. Epilepsia. 2005; 46:19–25. [PubMed: 15938707]
55. Soares JC, Kochunov P, Monkul ES, et al. Structural brain changes in bipolar disorder using deformation field morphometry. Neuroreport. 2005; 16:541–544. [PubMed: 15812303]

56. Artiges E, Ricalens E, Berthoz S, Krebs MO, Penttilä J, Trichard C, Martinot JL. Exposure to smoking cues during an emotion recognition task can modulate limbic fMRI activation in cigarette smokers. Addict Biol. 2009; 14:469–77. [PubMed: 19650816]
57. Hong LE, Gu H, Yang Y, Ross TJ, Salmeron BJ, Buchholz B, Thaker GK, Stein EA. Association of nicotine addiction and nicotine's actions with separate cingulate cortex functional circuits. Arch Gen Psychiatry. 2009; 66:431–41. [PubMed: 19349313]
58. Saccone KA, George TP, Head CA, Vessichio JC, Easton CJ, Prigerson HG. Adverse childhood experiences, smoking and mental illness in adulthood: a preliminary study. Ann Clin Psychiatry. 2007; 19:89–97. [PubMed: 17612848]
59. Jackson KM, Sher KJ, Cooper ML, Wood PK. Adolescent alcohol and tobacco use: onset, persistence, and trajectories of use across two samples. Addiction. 2002; 97:517–531. [PubMed: 12033653]
60. Patton GC, Coffey C, Carlin JB, Sawyer SM, Lynskey M. Reverse gateways? Frequent cannabis use as a predictor of tobacco initiation and nicotine dependence. Addiction. 2005; 100:1518–1525. [PubMed: 16185213]
61. Strakowski SM, DelBello MP, Fleck DE, Adler CM, Anthenelli RM, Keck PE Jr, Arnold LM, Amicone J. Effects of co-occurring cannabis use disorders on the course of bipolar disorder after a first hospitalization for mania. Arch Gen Psychiatry. 2007; 64:57–64. [PubMed: 17199055]
62. Strakowski SM, DelBello MP, Fleck DE, Adler CM, Anthenelli RM, Keck PE Jr, Arnold LM, Amicone J. Effects of co-occurring alcohol abuse on the course of bipolar disorder following a first hospitalization for mania. Arch Gen Psychiatry. 2005; 62:851–8. [PubMed: 16061762]
63. Goldstein BI, Fagiolini A, Houck P, Kupfer DJ. Cardiovascular disease and hypertension among adults with bipolar I disorder in the United States. Bipolar Disord. 2009; 11:657–662. [PubMed: 19689508]
64. Anthenelli RM. Treating patients with bipolar disorder and COPD or asthma. Supplement to Current Psychiatry. 2005; 4:34–42.
65. Carney CP, Jones LE. Medical comorbidity in women and men with bipolar disorders: a population-based controlled study. Psychosom Med. 2006; 68:684–691. [PubMed: 17012521]
66. Elmslie JL, Silverstone JT, Mann JI, Williams SM, Romans SE. Prevalence of overweight and obesity in bipolar patients. J Clin Psychiatry. 2000; 61:179–184. [PubMed: 10817102]
67. Fagiolini A, Frank E, Scott JA, Turkin S, Kupfer DJ. Metabolic syndrome in bipolar disorder: findings from the Bipolar Disorder Center for Pennsylvanians. Bipolar Disord. 2005; 7:424–430. [PubMed: 16176435]
68. Simon GE, Von Kerff M, Saunders K, Miglioretti DL, Crane PK, van Belle G, Kessler RK. Association between obesity and psychiatric disorders in the US adult population. Arch Gen Psychiatry. 2006; 63:824–830. [PubMed: 16818872]
69. Heffner, JL.; Winders-Barrett, S.; Anthenelli, RM. Obesity and smoking. In: McElroy, SL.; Allison, DB.; Bray, GA., editors. Obesity and Mental Disorders. New York: Taylor & Francis; 2006. p. 123-144.
70. Zevin S, Benowitz NL. Drug interactions with tobacco smoking: an update. Clin Pharmacokinet. 1999; 36:425–438. [PubMed: 10427467]
71. Bigos KL, Pollock BG, Coley KC, Miller DD, Marder SR, Aravagiri M, et al. Sex, race, and smoking impact olanzapine exposure. J Clin Pharmacol. 2008; 48:157–165. [PubMed: 18199892]
72. Rostami-Hodjegan A, Amin AM, Spencer EP, Lennard MS, Tucker GT, Flanagan RJ. Influence of dose, cigarette smoking, age, sex, and metabolic activity on plasma clozapine concentrations: a predictive model and nomograms to aid clozapine dose adjustment and to assess compliance in individual patients. J Clin Psychopharmacol. 2004; 24:70–78. [PubMed: 14709950]
73. Spigset O, Carleborg L, Hedenmalm K, et al. Effect of cigarette smoking on fluvoxamine pharmacokinetics in humans. Clin Pharmacol Ther. 1995; 58:399–403. [PubMed: 7586931]
74. Haslemo T, Eikeseth PH, Tanum L, Molden E, Refsum H. The effect of variable cigarette consumption on the interaction with clozapine and olanzipine. Eur J Clin Pharmacol. 2006; 62:1049–1053. [PubMed: 17089108]

75. Jain S, Chawla JM, Theethira TG, Strassnig M, Chengappa KNR. Changes in cigarette consumption in psychiatric patients: impact on side-effects or the efficacy of clozapine and olanzipine. Acta Neuropsychiatrica. 2008; 20:324–326.

76. Zullino DF, Delessert D, Eap CB, Preisig M, Baumann P. Tobacco and cannabis smoking cessation can lead to intoxication with clozapine or olanzipine. Int Clin Psychopharmacol. 2002; 17:141–143. [PubMed: 11981356]

77. Killen JD, Fortman SP, Schatzberg A, Hayward C, Varady A. Onset of major depression during treatment for nicotine dependence. Addict Behav. 2003; 28:461–470. [PubMed: 12628619]

78. Hitsman B, Borrelli B, McChargue DE, Spring B, Niaura R. History of depression and smoking cessation outcome: a meta-analysis. J Consult Clin Psychol. 2003; 71:657–663. [PubMed: 12924670]

79. Berlin I, Covey LS. Pre-cessation depressive mood predicts failure to quit smoking: The role of coping an personality traits. Addiction. 2006; 101:1814–1821. [PubMed: 17156181]

80. Niaura R, Britt DM, Borelli B, Shadel WG, Abrams DB, Goldstein MG. History and symptoms of depression among smokers during a self-initiated quit attempt. Nicotine Tob Res. 1999; 1:251–257. [PubMed: 11072422]

81. Kenford SL, Smith SS, Wetter DW, Jorenby DE, Fiore MC, Baker TB. Predicting relapse back to smoking: Contrasting affective and physical models of dependence. J Consult Clin Psychol. 2002; 70:216–227. [PubMed: 11860048]

82. Doran N, Spring B, McChargue D, Pergadia M, Richmond M. Impulsivity and smoking relapse. Nicotine Tob Res. 2004; 6:641–7. [PubMed: 15370160]

83. Burton SM, Tiffany ST. The effect of alcohol consumption on craving to smoke. Addiction. 1997; 92:15–26. [PubMed: 9060194]

84. Humfleet G, Muñoz R, Sees K, Reus V, Hall S. History of alcohol or drug problems, current use of alcohol or marijuana, and success in quitting smoking. Addict Behav. 1999; 24:149–154. [PubMed: 10189984]

85. Kahler CW, Spillane NS, Metrik J. Alcohol use and initial smoking lapses among heavy drinkers in smoking cessation treatment. Nicotine Tob Res. 2010; 12:781–785. [PubMed: 20507898]

86. Leeman RF, McKee SA, Toll BA, Krishnan-Sarin S, Cooney JL, Makuch RW, O'Malley SS. Risk factors for treatment failure in smokers: relationship to alcohol use and to lifetime history of an alcohol use disorder. Nicotine Tob Res. 2008; 10:1793–1809. [PubMed: 19023831]

87. Ford DE, Vu HT, Anthony JC. Marijuana use and cessation of tobacco smoking in adults from a community sample. Drug Alcohol Depend. 2002:243–248. [PubMed: 12127195]

88. Gourlay SG, Forbes A, Marriner T, Pethica D, McNeil JJ. Prospective study of factors predicting outcome of transdermal nicotine treatment in smoking cessation. BMJ. 1994; 309:842–846. [PubMed: 7950614]

89. Salloum IM, Cornelius JR, Mezzich JE, Kirisci L. Impact of concurrent alcohol misuse on symptom presentation of acute mania at initial evaluation. Bipolar Disord. 2002; 4:418–421. [PubMed: 12519103]

90. Fiore, MC.; Jaén, CR.; Baker, TB., et al. Treating tobacco use and dependence: 2008 Update. Rockville, MD: U.S. Department of Health and Human Services; Clinical practice guideline.

91. Breslau N, Kilbey M, Andreski P. Nicotine withdrawal symptoms and psychiatric disorders: findings from an epidemiologic study of young adults. Am J Psychiatry. 1992; 149:464–469. [PubMed: 1554030]

92. Xian H, Scherrer JF, Madden PAF, Lyons MJ, Tsuang M, True WR, Eisen SA. Latent class typology of nicotine withdrawal: genetic contributions and association with failed smoking cessation and psychiatric disorders. Psychol Med. 2005:409–419. [PubMed: 15841876]

93. Xian H, Scherrer JF, Eisen SA, Lyons MJ, Tsuang M, True WR, Bucholz KK. Nicotine dependence subtypes: association with smoking history, diagnostic criteria and psychiatric disorders in 5440 regular smokers from the Vietnam Era Twin Registry. Addictive Behav. 2007; 32:137–147.

94. Foulds J, Gandhi KK, Steinberg MB, Richardson DL, Williams JM, Burke MV, Rhoads GG. Factors associated with quitting smoking at a tobacco dependence treatment clinic. Am J Health Behav. 2006; 30:400–412. [PubMed: 16787130]

95. Klesges RC, Winders SE, Meyers AW, Eck LH, Ward KD, Hultquist CM, et al. How much weight gain occurs following smoking cessation? A comparison of weight gain using both continuous and point prevalence abstinence. J Consult Clin Psychol. 1997; 65:286–291. [PubMed: 9086692]

96. Brouwer RJ, Pomerleau CS. "Prequit attrition" among weight-concerned women smokers. Eat Behav. 2000; 1:145–151. [PubMed: 15001057]

97. Copeland AL, Martin PD, Geiselman PJ, Rash CJ, Kendzor DE. Predictors of pretreatment attrition from smoking cessation among pre- and postmenopausal, weight-concerned women. Eat Behav. 2006; 7:243–251. [PubMed: 16843227]

98. Meyers AW, Klesges RC, Winders SE, Ward KD, Peterson BA, Eck LH. Are weight concerns predictive of smoking cessation? A prospective analysis. J Consult Clin Psychol. 1997; 65(3):448–452. [PubMed: 9170768]

99. Gulliver SB, Wolfsdorf BA, Morissette SB. Treating tobacco dependence: development of a smoking cessation program for outpatient mental health clinics. Cog Behav Practice. 2004; 11:315–330.

100. Dale LC, Olsen DA, Patten CA, Schroeder DR, Croghan IT, Hurt RD, Offord KP, Wolter TD. Predictors of smoking cessation among elderly smokers treated for nicotine dependence. Tob Control. 1997; 6:181–187. [PubMed: 9396101]

101. Carlson LE, Taenzer P, Koopmans J, Bultz BD. Eight-year follow-up of a community-based large group behavioral smoking cessation intervention. Addict Behav. 2000; 25:725–741. [PubMed: 11023014]

102. Matheny KB, Weatherman KE. Predictors of smoking cessation and maintenance. J Clin Psychol. 1998; 54:223–235. [PubMed: 9467767]

103. Murray RP, Gerald LB, Lindgren PG, Connett JE, Rand CS, Anthonisen NR. Characteristics of participants who stop smoking and sustain abstinence for 1 and 5 years in the Lung Health Study. Prev Med. 2000; 30:392–400. [PubMed: 10845748]

104. Himelhoch S, Daumit G. To whom do psychiatrists offer smoking-cessation counseling? Am J Psychiatry. 2003; 160:2228–2230. [PubMed: 14638595]

105. Phillips KM, Brandon TH. Do psychologists adhere to the clinical practice guidelines for tobacco cessation? A survey of practitioners. Prof Psychol Res Practice. 2004; 35:281–285.

106. Evins AE, Cather C, Culhane MA, Birnbaum A, Horowitz J, Hsieh E, Freudenreich O, Henderson DC, Schoenfield DA, Rigotti NA, Goff DC. A 12-week, double-blind, placebo-controlled study of bupropion SR added to high-dose dual nicotine replacement therapy for smoking cessation or reduction in schizophrenia. J Clin Psychopharmacol. 2007; 27:380–386. [PubMed: 17632223]

107. George TP, Vessicchio JC, Sacco KA, Weinberger AH, Dudas MM, Allen TM, Creeden CL, Potenza MN, Feingold A, Jatlow PI. A placebo-controlled trial of bupropion combined with nicotine patch for smoking cessation in schizophrenia. Biol Psychiatry. 2008; 63:1092–1096. [PubMed: 18096137]

108. Borelli B, Niaura R, Keuthen NJ, Goldstein MG, DePue JD, Murphy C, Abrams DB. Development of major depressive disorder during smoking-cessation treatment. J Clin Psychiatry. 1996; 57:534–538. [PubMed: 8968303]

109. Patten CA, Rummans TA, Croghan IT, Hurt RD, Hays JT. Development of depression during placebo-controlled trials of bupropion for smoking cessation: case reports. J Clin Psychiatry. 1999; 60:436–441. [PubMed: 10453796]

110. Tsoh JY, Humfleet Gl, Muñoz RF, Reus VI, Hartz DT, Hall SM. Development of major depression after treatment for smoking cessation. Am J Psychiatry. 2000; 157:368–374. [PubMed: 10698811]

111. Hollen V, Ortiz G, Schacht L, Mojarrad MG, Lane GM Jr, Parks JJ. Effects of adopting a smoke-free policy in state psychiatric hospitals. Psychiatr Serv. 2010; 61:899–904. [PubMed: 20810588]

112. Shmueli D, Fletcher L, Hall SE, Hall SM, Prochaska JJ. Changes in psychiatric patients' thoughts about quitting smoking during a smoke-free hospitalization. Nicotine Tob Res. 2008; 10:875–881. [PubMed: 18569762]

113. Moss TG, Weinberger AH, Vessicchio JC, Mancuso V, Cushing SJ, Pett M, Kitchen K, Selby P, George TP. A tobacco reconceptualization in psychiatry: toward the development of tobacco-free psychiatric facilities. Am J Addict. 2010; 19:293–311. [PubMed: 20653636]

114. Prochaska JJ, Delucchi K, Hall SM. A meta-analysis of smoking cessation interventions with individuals in substance abuse treatment or recovery. J Consult Clin Psychol. 2004; 72:1144–1156. [PubMed: 15612860]
115. Tsoi DT, Porwal M, Webster AC. Interventions for smoking cessation and reduction in individuals with schizophrenia. Cochrane Database Syst Rev. 2010; 16:CD007253. [PubMed: 20556777]
116. Smith SS, McCarthy DE, Japuntich SJ, Christianson B, Piper ME, Jorenby DE, Fraser DL, Fiore MC, Baker TB, Jackson TC. Comparative effectiveness of 5 smoking cessation pharmacotherapies in primary care clinics. Arch Intern Med. 2009; 169:2148–2155. [PubMed: 20008701]
117. Ketter TA, Jenkins JB, Schroeder DH, Pazzaglia PJ, Marangell LB, George MS, Callahan AM, Hinton ML, Chao J, Post RM. Carbamazepine but not valproate induces bupropion metabolism. J Clin Psychopharmacol. 1995; 15:327–333. [PubMed: 8830063]
118. Post RM, Altschuler LL, Leverich GS, Frye MA, Nolen WA, Kupka RW, Suppes T, McElroy S, Keck PE, Denicoff KD, Grunze H, Walden J, Kitchen CMR, Mintz J. Mood switch in bipolar depression: comparison of adjunctive venlafaxine, bupropion and sertraline. Br J Psychiatry. 2006; 189:124–131. [PubMed: 16880481]
119. Truman CJ, Goldberg JF, Ghaemi SN, Baldassano CF, Wisniewski SR, Dennehy EB, Thase ME, Sachs GS. Self-reported history of manic/hypomanic switch associated with antidepressant use: data from the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). J Clin Psychiatry. 2007; 68:1472–1479. [PubMed: 17960960]
120. Gonzales D, Rennard SI, Nides M, Oncken C, Azoulay S, Billing CB, Watsky EJ, Gong J, Williams KE, Reeves KR. Varenicline Phase 3 Study Group. Varenicline, an α4β2 nicotinic acetylcholine receptor partial agonist, vs. bupropion and placebo for smoking cessation: A randomized controlled trial. JAMA. 2006; 296:47–55. [PubMed: 16820546]
121. Jorenby DE, Hays JT, Rigotti NA, Azoulay S, Watsky EJ, Williams KE, Billing CB, Gong J, Reeves KR. Efficacy of varenicline, an α4β2 nicotinic acetylcholine receptor partial agonist, vs. placebo or sustained-release bupropion for smoking cessation. JAMA. 2006; 296:56–63. [PubMed: 16820547]
122. DiPaula BA, Thomas MD. Worsening psychosis induced by varenicline in a hospitalized psychiatric patient. Pharmacotherapy. 2009; 29:852–857. [PubMed: 19558259]
123. Kohen I, Kremen N. Varenicline-induced manic episode in a patient with bipolar disorder. Am J Psychiatry. 2007; 164:1269–1270. [PubMed: 17671294]
124. Morstad AE, Kutscher EC, Kennedy WK, Carnahan RM. Hypomania with agitation associated with varenicline use in bipolar disorder. Ann Pharmacotherapy. 2008; 42:288–289.
125. Brown RA, Kahler CW, Niaura R, Abrams DB, Sales SD, Ramsey SE, Goldstein MG, Burges ES, Miller IW. Cognitive-behavioral treatment for depression in smoking cessation. J Consult Clin Psychol. 2001; 69:471–480. [PubMed: 11495176]
126. Hall SM, Muñoz RF, Reus VI, Sees KL, Duncan C, Humfleet GL, Hartz DT. Mood management and nicotine gum in smoking treatment: a therapeutic contact and placebo-controlled study. J Consult Clin Psychol. 1996; 64:1003–1009. [PubMed: 8916629]
127. Williams JM, Steinberg ML, Zimmerman MH, Gandhi KK, Stipelman B, Budsock PD, Ziedonis DM. Comparison of two intensities of tobacco dependence counseling in schizophrenia and schizoaffective disorder. J Subst Abuse Treat. 2010; 38:384–393. [PubMed: 20363089]
128. Hall SM, Muñoz RF, Reus VI. Cognitive-behavioral intervention increases abstinence rates for depression-history smokers. J Consult Clin Psychol. 1994; 62:141–146. [PubMed: 8034816]
129. Patten CA, Martin JE, Myers MG, Calfas KJ, Williams CD. Effectiveness of cognitive-behavioral therapy for smokers with histories of alcohol dependence and depression. J Stud Alcohol. 1998; 59:327–335. [PubMed: 9598714]
130. Hall SM, Reus VI, Muñoz RF, Sees KL, Humfleet GL, Hartz DT, Frederick S, Triffleman E. Nortripyline and cognitive-behavioral therapy in the treatment of cigarette smoking. Arch Gen Psychiatry. 1998; 55:683–690. [PubMed: 9707377]

131. Haas AL, Muňoz RF, Humfleet GL, Reus VI, Hall SM. Influences of mood, depression history, and treatment modality on outcomes in smoking cessation. J Consult Clin Psychol. 2004; 72:563–570. [PubMed: 15301640]

132. Joseph AM, Willenbring ML, Nugent SM, Nelson DB. A randomized trial of concurrent versus delayed smoking intervention for patients in alcohol dependence treatment. J Stud Alcohol. 2004; 65:681–691. [PubMed: 15700504]

133. Anthenelli RM. How—and why—to help psychiatric patients stop smoking. Current Psychiatry. 2005; 4:77–87.

Table 1

Potential Challenges of Smoking Cessation for Individuals with Bipolar Disorder

Domain	Challenge
Symptoms of bipolar disorder	• Vulnerability to depression, increased risk of postcessation negative affect • Impulsivity associated with mania/hypomania
Alcohol and drug use	• Substance-induced craving to smoke, increased likelihood of smoking relapse • Psychiatric instability stemming from substance use and its effects on medication adherence
Nicotine dependence and withdrawal	• Higher prevalence of heavy smoking • Greater severity of nicotine dependence and withdrawal • Postcessation weight gain may not be well-tolerated in combination with weight gain caused by psychotropic medications
Social support for quitting	• High exposure to smokers in the social environment • Limited partner support for smoking cessation
Beliefs and practices of mental health treatment providers and organizations	• Historical precedent of ignoring or encouraging tobacco use in mental health settings • Concerns that smoking cessation will lead to onset of a frank mood episode • Lower priority given to cigarette smoking as a treatment issue • Reluctance to address smoking because of inadequate training, poor compensation for tobacco treatment, or personal smoking status

Table 2

Overview of First-line Pharmacotherapies for Smoking Cessation and Their Potential Advantages and Disadvantages for Smokers with Bipolar Disorder

Medication	Efficacy (OR vs. placebo at 6 mos., with 95% CI)	Potential Advantages	Potential Disadvantages
Nicotine replacement therapy (NRT)		• Combination NRT among the most efficacious therapies • Few contraindications or medication interactions • Demonstrated safety/efficacy in other psychiatric populations • Nicotine gum may delay postcessation weight gain	• Possibility of inadequate replacement, particularly in these likely heavy smokers using a single formulation at the standard dose • Increased cost of combination NRT
Patch (6–14 wks):	1.9 (1.7–2.2)		
Gum (6–14 wks):	1.5 (1.2–1.7)		
Lozenge (2 mg):	2.0 (1.4–2.8)		
Nasal spray:	2.3 (1.7–3.0)		
Inhaler:	2.1 (1.5–2.9)		
Combination NRT[1]:	3.6 (2.5–5.2)		
Bupropion SR		• May delay postcessation weight gain • Demonstrated safety/efficacy in other psychiatric populations	• Medication interactions • Possibility of inducing mania/hypomania • Other potential neuropsychiatric side effects
Monotherapy:	2.0 (1.8–2.2)		
Bupropion + nicotine patch:	2.5 (1.9–3.4)		
Varenicline	3.1 (2.5–3.8)	• Most efficacious of the monotherapies • No significant medication interactions known	• Potential neuropsychiatric side effects

Note: Efficacy data are from the updated Clinical Practice Guidelines (Fiore et al., 2008). OR=odds ratio; CI=confidence interval.

[1]Refers to the combination of the long-acting nicotine patch (>14 weeks) with the shorter-acting nicotine gum or nasal spray.